SCIENTIFIC SECTION

ANTIDOTES. III. THALLIUM.*

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In 1924 laboratory investigations suggested the value of thallium in the control of various rodents. Field tests conducted in the next few years validated our laboratory conclusions (19, 21). Literature did not reveal any definite information regarding antidotes for thallium poisoning, so studies along this line were undertaken. These experiments were conducted in the Washington laboratory of the Bureau of Chemistry (now called the Food and Drug Administration) of the United States Department of Agriculture at an elevation of about one hundred feet above sea-level. Thallium sulphate solutions were included in the diet, or injected subcutaneously or intravenously into dogs. Less extensive studies were made on rabbits, rats, guinea-pigs and cats. Dogs used in this work were fed 100 Gm. of ground lean meat containing five per cent of dried whole milk powder daily. Bones were included in the diet once a week. Drinking water was available at all times. No evidence of dietary disease was noted among the control animals. The development of thallotoxicosis was followed daily and definite symptoms were recognized as characteristic of thallium poisoning (9, 16, 18, 20). In some experiments the protective procedure was commenced at the time poison was administered. In other experiments treatment was delayed. Chemical studies of thallium elimination under various methods of treatment were contemplated, but were not carried out in detail then because of the lack of suitable analytical methods. With the development of quantitative methods, chemical essays are used to control the efficiency of various procedures.

TABLE I.—CERTAIN LETHAL DOSE OF THALLIUM—MG. TL PER KG.

Animals.	Method of Administration. Oral.	Subcutaneous.	Intraperitoneal.	Intravenous.
Frogs	....	2.5–60 (?)	...	...
		150 (3)		
Birds	35–50	40–160	...	...
Mice	25 (5)	70 (2)	70 (2)	...
			30 (4)	
Rats	25 (5)	60 (2)	60 (1)	
			40 (2)	20–25
Guinea pigs	....	70 (2)	70 (1)	
		10 (5)	10 (5)	25
Rabbits	500	20–60	...	25 (1)
Hedgehogs	....	36	...	...
Cats	250–500	15	...	...
Dogs	15–100	15–45	13	20–25

Foot-note: The figures in parentheses represent the day's interval between injection and death.

The intravenous administration of 25 mg. of thallium per kilo (in the form of thallium sulphate) was followed by death within five to ten days, and this was

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selected as the certain lethal dose (L. D. 100). Smaller doses occasionally killed, although the percentage of recoveries increased as the dose decreased. Twenty-five mg. of thallium per kilo fed to rats or intravenously injected in the marginal ear vein of rabbits produced death within three to five days (21). Available results upon toxicity to various animals are given in Table I.

Based on a knowledge of the chemical behavior and toxicity of thallium compounds, various drugs were administered in attempts to counteract the poisonous effects.

(1) *Sodium thiosulphate* had been considered as an antidote in the treatment of heavy metal poisoning, although in 1924 no references to its use in thallotoxicosis were found. Our original tests failed to show definite relief following its use. Oral administration had very little effect. Intravenous injections often increased the severity of thallium symptoms within twenty-four hours. The following year Buschke and Peiser (5, 7, 8) published their study on this question and reached the same conclusion.

(2) The insolubility of the *halides* of thallium led to the study of the possibility of protecting animals by a course of treatment with the chloride or iodide of sodium or potassium. The potassium salts were useful but caused cardiac depression. Administration of sodium chloride was somewhat less effective than sodium iodide. The elimination of thallium was followed by flame tests on twenty-four hour urine samples to determine the relative intensity of green color. Treatment with sodium iodide decreased, and treatment with sodium thiosulphate increased the thallium excretion in the urine.

(3) One outstanding feature of thallium poisoning is the general endocrinological depression. Various endocrine stimulants were considered and finally *pilocarpine* was adopted because of its low toxicity in effective doses. Not only does pilocarpine serve as an endocrine stimulant, but also it stimulates perspiration. As thallium is eliminated in the sweat, this was believed to reduce the strain on the kidneys.

(4) Thallium poisoning produces hypo- or achlorhydria (13, 14, 15, 21). Therefore, *hydrochloric acid* was given by mouth to dogs with some success, as an adjunct to other methods of treatment.

(5) Marked disturbances of *calcium* metabolism have been observed in thallotoxicosis. Our studies did not indicate any particular benefit following the administration of calcium salts alone, but in conjunction with iodide-thiosulphate treatment appeared to favor more rapid recovery.

(6) Subsequent reports of studies on treatment suggested and denied the value of various *glandular extracts*, more particularly thymus, parathyroid and pituitary gland extracts (1, 2, 3, 6, 8, 9, 10, 11, 14, 15, 17, 21, 22, 23, 24). No laboratory studies were made with glandular extracts in the 1924 investigations. The incorporation of various glandular extracts in the treatment of thallium poisoning to dogs in later studies did not appear to be successful.

Based on results obtained in the 1924 animal experiments, it was felt that thallium poisoning would be combated most successfully by: (*a*) intravenous administration of sodium iodide until thallium had practically disappeared from the twenty-four hour urine; (*b*) sodium thiosulphate intravenously to induce gradual elimination of thallium; (*c*) pilocarpine and calcium salts intravenously; and (*d*)

oral administration of hydrochloric acid. This regime based solely upon tests on animals may be inadequate, since there is always a question regarding the efficacy of an antidote *for* humans, unless it is firmly established by experiments *upon* humans. Recognized methods of treating strychnine or arsenic poisoning which were developed upon animals have shown somewhat disappointing results when employed upon man, and vice versa. The need for extreme caution in advocating any specific course of treatment as "a successful antidote" for any poison is appreciated. For this reason this regime was not included in the 1931 report (21) in which reference was made to the use of iodides or chlorides and to sodium thiosulphate intravenously.

What results have been obtained in treating human thallotoxicosis? Thallium is commonly, or at least frequently used in medicine. Of 8006 children who received thallium acetate as a depilatory, 447 were poisoned and 8 died. A number of reports of clinical, cosmetic, rodenticidal and suicidal thallium poisoning have been collected.

The extensive survey by Buschke and Peiser (9) contains several reports of attempts to counteract human thallotoxicosis. Bogdanov and Lasko (4) relieved pains in the extremities in two cases of thallium poisoning by sodium thiosulphate; Mrongowius and Duchan (18) in 1928, and Caluzzi (12) in 1929, observed a decrease in toxicity of thallium salts to older children by administration of 1 to 1.5 Gm. of sodium thiosulphate three times daily. Subsequent administration of sodium thiosulphate accelerated recovery following clinical use of thallium. For the treatment of thallotoxicosis Mrongowius and Duchan (18) recommended a combination of 5 Gm. of sodium thiosulphate and 5 mg. of pilocarpine nitrate in 20 cc. of distilled water. It is of interest, in this connection, that Buschke, Duchan and Joseph (7) were unable to obtain any benefit by using this treatment upon thallium-poisoned animals.

Over thirty-one persons were poisoned by thallium in January 1932, near Fresno, California (16, 20), at an elevation of two hundred feet above sea-level. Fourteen were hospitalized, one being less seriously poisoned than the others. Eight patients who were treated by this regime recovered. Six others who were treated with sodium thiosulphate, dextrose and parathyroid extract died. It is not certain that these eight patients would have died if this regime had not been followed; however, in the opinion of the attending physicians their clinical condition was as serious as the condition of those who died.

CONCLUSIONS.

1. Experiments upon animals in 1924 led to the development of a definite method for combating thallotoxicosis: treatment with sodium iodide, sodium thiosulphate, pilocarpine, calcium salts and hydrochloric acid.

2. This regime was successful in treating eight humans poisoned by thallium; six untreated patients died.

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CERTAIN POISONOUS PLANTS OF WYOMING ACTIVATED BY SELENIUM AND THEIR ASSOCIATION WITH RESPECT TO SOIL TYPES.

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In 1917, the senior author published a brief treatise[1] on the poisonous properties of the two-grooved milk vetch (*Astragalus bisulcatus*). The toxic principles

[1] Wyoming Experiment Station Bulletin 112.